



6/15

Fig 6A

1 atggcgccg aagcctcgga gagcgggcca gcgctgcatg agctcatgog cgaggcggag
61 atcagcctgc tcgagtgcaa ggtgtgcttt gagaagtttg gccaccggca gcagcggcgc
121 ccgcgcaacc tgtcctgagg ccacgtgggc tgccctggcct gcgtggccgc cctggcgcac
181 ccgcgcactc tggccctcga gtgccattc tgcaggcgag ctgcccggg ctgcgacacc
241 agcgactgcc tgccggtgct gcacctcata gagctcctgg gctcagcgct tcgccagtc
301 ccggccgccc atcgccgcgc cccagcgcc cccggagccc tcacctgcca ccacacctc
361 ggcggtgagg ggacctggt caacccacc ggactggcgc tttgtccaa gacggggcgt
421 gtcgtggtgg tgcacgacgg caggaggcgt gtcaagattt ttgactcagg gggaggatgc
481 gcgcatcagt ttggagagaa gggggacgct gcccagaca ttaggtaccc tgtggatgtc
541 accatcacca acgactgcca tgtggtgtc actgacgccg gcgatcgctc catcaaagt
601 tttgattttt ttggccagat caagctgtc attggaggcc aattctcctt accttgggt
661 gtggagacca cccctcagaa tgggattgtg gtaactgatg cggaggcagg gtccctgcac
721 ctcttgagc tcgacttcgc ggaaggggtc ctccggagaa ctgaaagggt gcaagctcat
781 ctgtgcaatc cccgaggggt ggcagtgtct tggctcaccg gggccattgc ggtcctggag
841 cccccctgg ccctggggac tggggtttgc agcaccaggg tgaaagtgtt tagctcaagt
901 atgcagcttg tcggccaagt ggatacctt gggtgagcc tctactttcc ctccaaaata
961 actgcctccg ctgtgacctt tgatcaccag ggaatgtga ttgttgaga tacatctggt
1021 ccagctatcc tttgcttagg aaaacctgag gagtttcag taccgaagcc catggtcact
1081 catggtcttt cgcatcctgt ggctcttacc ttcaccaagg agaattctct tcttgtgctg
1141 gacacagcat ctcttctat aaaagtctat aaagttgact gggggtgatg ggctggggtg
1201 ggtccctgga atcagaagca ctagtctgc cattaatgaa ttgtttaacc ctggataagt
1261 cacttaaaact catctatcca ggcagggata attaaaacca tctggcagac ttacaaagct
1321 tgggacagtt attggagatt aatctaccat ttattgaatg catactctgt gcaaggaaat
1381 ttgcaaatat tagcttattt aatctgtact atccagttag gtaatttctt cccccccaag
1441 atagagtcaa gctctgtcac ccagggtgga gtgcagaagc atgatcacag ctactacag

SEQ ID NO: 1

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Fig 6B

EPM2B protein sequence

MAAEASESGPALHELMREAEISLLECKVCFEKFQRRPRNLSCGHVV
CLACVAALAHPRTLALECPFCRRACRGCDTSDCLPVLHLIELLSALRQS
PAAHRAAPSAPGALTCHHTFGGWGTLVNPTGLALCPKTGRVVVVDGRRR
VKIFDSGGGCAHQFGEKGDAQAQDIRYPVDVTTTNDCHVVVTDAGDRSIK
FDFFGQIKLVIGGQFSLPWGVETTPQNGIVVTDAGSLHLLDVDFAEV
LRRTERLQAHLNPRGVAVSWLTGAIAVLEHPLALGTGVCSTRVKVFSS
MQLVGQVDTFGLSLYFPSKITASAVTFDHQGNVIVADTSGPAILCLGKPE
EFPVPKPMVTHGLSHPVALTFTKENSLLVLDTASHSIKVYKVDWG

SEQ ID NO: 2

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Fig 7A

Promoter (5') sequence:

```
1  CCCCCAAGGCC CCCCCGGCCCC CCAGGCAACC CCAGGCCCCC AGGCAACCCA
51  AGGCCCCCCC GCCCAAGGCC CCCAGGTTT CCGGCCCCAA GAACCAAGCC
101 CCCCCGCCCC CCGCCCCCAG CACCCAGCAC CAAGCCCCCG CCCCCCGCCC
151 CAAGCACCCA GCCCAGCAC CCAGCCCCCG CCCCAGCCCC AGCCCCAGCA
201 CCCAGCCCCC GCCCAGCAC CCAGCCCCAG CACCCAGCCC CCGCCCCAGC
251 CCCAGCCCCC GTCCCCCCCC CCAGCACCCA GCCCCAGCCC CAGCAGCAGC
301 ACCCAGCAGG GGACTGCAAA GCGTAGGCTA CCCCAGGTGG AACACCGTGT
351 TCTAGTTTTG CTTTGCCGTT TGCAGCCTGG GCGATCGGGG GCCACCGCTC
401 GAGCCTGTTT CCGTGC GCGG AAAGCGGAGC CGCCCCGCCC CGCCCCCGCC
451 CTGCCTGAAG GTCACGGGCC TGGGCCTGCG GCGCGCGGTG CGGCCCGCGA
501 GCGTCCGCTC CCGCGCCCTC CGCAGTCAGC GCCCCCGCCG CCGCCGGGGG
551 ACCGCAGGCC GCGGCCGAGA GGCTGCGCGC TGCGCCCCGC ACGTCAAGGC
601 CCGCCCCGCC CCGCCCCGCC CCGTGACCGG CCCCGGCCCC GGCCCCGGCC
651 CCGGCCCGCG ACCGAGCGGC GCCCGCGGGA GCGGCGGCGG CCGCGCG
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Coding sequence:

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ATG
701 GGGGCCGAAG CGGCGGGGAG CGGGCGGGCG CTGCGGGAGC TGGTGCGCGA
751 GGCCGAGGTC AGCTTGCTCG AGTGCAAGGT GTGCTTCGAG AGGTTGCGCC
801 ACCGCCAGCA GCGGCGCCCC CGCAACCTGC CTTGCGGCCA CGTGGTGTGC
851 CTGGCCTGCG TGGCGGCCCT GCGGCACCCG CGGACGCTGG CCTGGAGTGT
901 CCCCCTCTGC CGCCGGGCCCT GCGCGGGCTG CGACACAGC GACTGCCTGC
951 CGGTGCTTCA CCTCTGGAG CTCTGGGCT CGGCGTGCG CCCAGCCCCC
1001 GCGGCCCCC CCGCGCCCC CCGCGCCCC CCTGCGCCC CGGGCGCCCT
1051 CGCCTGCCAT CACGCGTTCG GAGGCTGGGG GACCTGGTC AACCCACGG
1101 GGCTGGCGCT GTGCCCCAAG ACCGGGCGGG TCGTGGTGGT GCACGACGGC
1151 AGGAGGCGGG TCAAGATCTT TGAATCCGGG GGAGGATGCG CCCATCAGTT
1201 TGGAGAGAAG GGGGAGGCTG CCCAGGACAT TAGGTACCCC CTGGACGTGC
1251 CCGTCACCAA CCACTGCCAC GTGGTTGTCA CCGACGCCGG CGACCGCTCC
1301 ATCAAAGTGT TTGATTTCTT TGGCCAGATC AAGCTCGTCA TTGGAGACCA
1351 GTTTTCCTTA CCTTGGGCGG TGGAGACCAC CCCTCAGAAT GGGGTCTGGG
1401 TAACTGACGC CGAGGCAGGG TCGCTGCACC TGCTGGAAGT CGACTTTGCA
1451 GAAGGAGCCC TCCAGAGGAC TGAAAAGCTG CAAGGTCATC TGTGCAACCC
1501 GCGAGGGGTG GCCGTGTCTT GGCTCACTGG GGCCATTGCG GTCCTGGAGC
1551 ACCCTCCGGG GCTGGGGGCT GGGGCGGGCA GCACCGCCGT GAAGGTGTTT
1601 AGCCCAACTA TGCACTGAT CGGCCAGGTG GATACCTTTG GGCTCAGCCT
1651 CTTTTTCCCC TCTAGAATAA CCGCTCCGC CGTGACCTTT GATCACCAGG
1701 GGAATGTGAT TGTGCAAGT ACTTCTAGTC AGGCCGTCTT ATGCTTGGGA
1751 CAGCCTGAGG AATTTCCAGT CTTGAAGCCC ATCATCACCC ATGGTCTTTC
1801 CCATCCTGTG GCACTGACCT TCACCAAGGA GAATTTCTTT CTTGTGCTGG
1851 ACAGTGACGC CCATCCGTA AAAGTCTACA AGGCTGACTG GGGGTAA
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SEQ ID NO: 3

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Fig 7B

Met Gly Ala Glu Ala Ala Gly Ser Gly Arg Ala Leu Arg Glu Leu Val
1 5 10 15

Arg Glu Ala Glu Val Ser Leu Leu Glu Cys Lys Val Cys Phe Glu Arg
20 25 30

Phe Gly His Arg Gln Gln Arg Arg Pro Arg Asn Leu Pro Cys Gly His
35 40 45

Val Val Cys Leu Ala Cys Val Ala Ala Leu Ala His Pro Arg Thr Leu
50 55 60

Ala Leu Glu Cys Pro Phe Cys Arg Arg Ala Cys Arg Gly Cys Asp Thr
65 70 75 80

Ser Asp Cys Leu Pro Val Leu His Leu Leu Glu Leu Leu Gly Ser Ala
85 90 95

Leu Arg Pro Ala Pro Ala Ala Pro Arg Ala Ala Pro Arg Ala Ala Pro
100 105 110

Cys Ala Pro Gly Ala Leu Ala Cys His His Ala Phe Gly Gly Trp Gly
115 120 125

Thr Leu Val Asn Pro Thr Gly Leu Ala Leu Cys Pro Lys Thr Gly Arg
130 135 140

Val Val Val Val His Asp Gly Arg Arg Arg Val Lys Ile Phe Asp Ser
145 150 155 160

Gly Gly Gly Cys Ala His Gln Phe Gly Glu Lys Gly Glu Ala Ala Gln
165 170 175

Asp Ile Arg Tyr Pro Leu Asp Val Ala Val Thr Asn Asp Cys His Val
180 185 190

Val Val Thr Asp Ala Gly Asp Arg Ser Ile Lys Val Phe Asp Phe Phe
195 200 205

Gly Gln Ile Lys Leu Val Ile Gly Asp Gln Phe Ser Leu Pro Trp Gly
210 215 220

SEQ ID NO: 4

[illegible]

Fig 10

SEQ. ID NOS: 6-52

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Fig 6A



1 atggcgggccg aagcctcgga gagcgggcca gcgctgcatg agctcatgcg cgaggcggag
61 atcagcctgc tcgagtgcaa ggtgtgcttt gagaagtttg gccaccggca gcagcggcgc
121 ccgcgcaacc tgtcctgcgg ccacgtggtc tgccctggcct gcgtggccgc cctggcgcac
181 ccgcgcaactc tggccctcga gtgccattc tgcaggcgag cttgccgggg ctgcgacacc
241 agcgactgcc tgccggtgct gcacctcata gagctcctgg gctcagcgct tcgccagtc
301 ccggcgcgcc atcgcgccgc cccagcgcc cccggagccc tcacctgcca ccacaacctc
361 ggcggtgtgg ggacctggt caaccccaacc ggactggcgc tttgtccaa gacggggcgt
421 gtcgtggtgg tgcacgacgg caggaggcgt gtcaagattt ttgactcagg gggaggatgc
481 gcgcatacgt ttggagagaa gggggacgct gcccaagaca ttaggtaccc tgtggatgtc
541 accatcacca acgactgcca tgtggttgtc actgacgcgc gcgatcgctc catcaaagtg
601 tttgattttt ttggccagat caagcttgtc attggaggcc aattctcctt acctgggggt
661 gtggagacca cccctcagaa tgggattgtg gtaaactgatg cggaggcagg gtccctgcac
721 ctcttggaag tcgacttcgc ggaaggggtc ctccggagaa ctgaaagggtt gcaagctcat
781 ctgtgcaatc cccgaggggt ggcagtgtct tggctcaccg gggccattgc ggtcctggag
841 caccacctgg ccttggggac tggggtttgc agcaccaggg tgaaagtgtt tagctcaagt
901 atgcagcttg tcggccaagt ggataccttt gggtgagcc tctactttcc ctccaaaata
961 actgcctccg ctgtgacctt tgatcaccag ggaaatgtga ttgttgaga tacatctggt
1021 ccagctatcc tttgcttagg aaaacctgag gagtttccag taccgaagcc catggtcact
1081 catggtcttt cgcatactgt ggctcttacc ttcaccaagg agaattctct tcttgtgctg
1141 gacacagcat ctattctat aaaagtctat aaagttgact gggggtgatg ggtcgggggt
1201 ggtccctgga atcagaagca ctagtgtgc cattaatgaa ttgtttaacc ctggataagt
1261 cacttaaaact catctatcca ggcagggata attaaaacca tctggcagac ttacaaagct
1321 tgggacagtt attggagatt aatctaccat ttattgaatg cataactctgt gcaaggaaat
1381 ttgcaaatat tagcttattt aatctgtact atccagtgag gtaatttctt ccccccaag
1441 atagagtcaa gctctgtcac ccaggctgga gtgcagaagc atgatcacag ctactacag

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Fig 6B

EPM2B protein sequence

MAAEASESGPALHELMREAEISLLECKVCFEKFGHRQQRRPRNLSCGHVV
CLACVAALAHPRTLALECPFCRRACRGCDTSDCLPVLHLIELLGSALRQS
PAAHRAAPSAPGALTCHHTFGGWGTLVNPTGLALCPKTGRVVVVHDGRRR
VKIFDSGGGCAHQFGEKGDAAQDIRYPVDVTTTNDCHVVVTDAGDRSIKV
FDFFGQIKLVIGGQFSLPWGVETTPQNGIVVTD AEAGSLHLLDVDF AEGV
LRRTERLQAHL CNPRGVAVSWLTGAIAVLEHPLALGTGVCSTRVKVFSSS
MQLVGQVDTFGLSLYFPSKITASAVTFDHQGNVIVADTSGPAILCLGKPE
EFPVPKPMVTHGLSHPVALTFTKENSLLVLDTASHSIKVYKVDWG.

SEQ ID NO:2

9/15

Fig 7A

Promoter (5') sequence:

```
1  CCCCCAAGGCC CCCCCGGCCC CCAGGCAACC CCAGGCCCCC AGGCAACCCA
51  AGGCCCCCCG GCCCCAAGCC CCCCAGGTTT CCGGCCCCAA GAACCAAGCC
101 CCCC GGCCCC CCGCCCCAG CACCCAGCAC CAAGCCCCCG CCCCCCGCCC
151 CAAGCACCCA GCCCCAGCAC CCAGCCCCCG CCCCAGCCCC AGCCCCAGCA
201 CCCAGCCCCC GCCCCAGCAC CCAGCCCCAG CACCCAGCCC CCGCCCAGC
251 CCCAGCCCCC GTCCCCCCCC CCAGCACCCA GCCCCAGCCC CAGCAGCAGC
301 ACCCAGCAGG GGA CTGCAAA GCGTAGGCTA CCCCAGGTGG AACACCGTGT
351 TCTAGTTTTG CTTTGCCGTT TGCAGCCTGG GCGATCGGGG GCCACCGCTC
401 GAGCCTGTTT CCCGTCGCGG AAAGCGGAGC CGCCCCGCCC CGCCCCCGCG
451 CTGCCTGAAG GTCACGGGCC TGGGCTGCG GCGCGCGGTG CGGCCCGCGA
501 GCGTCCGCTC CCGCGCCCTC CGCAGTCAGC GCCCCGCCCG CCGCCGGGGG
551 ACCGCAGGCC GCGGCCGAGA GGCTGCGCG TCGGCCCGCG ACCTCAGGCC
601 CCGCCCCGCC CCGCCCCGCC CCGTGACCGG CCCC GGCCCC GGGCCCGGCC
651 CCGGCCCGCG ACCGAGCGGC GCGCGGGGA GCGGCGGCG CCGCGCG
```

Coding sequence:

```
ATG
701 GGGGCCGAAG CGGCGGGGAG CGGCGGGGCG CTGCGGGAGC TGGTGCGCGA
751 GGCCGAGGTC AGCTTGCTCG AGTGCAAGGT GTGCTTCGAG AGGTTGCGCC
801 ACCGCCAGCA GCGCGGCCCG CGCAACcTGC CCTGCGGCCA CGTGGTGTGC
851 CTGGCCTGCG TGGCGGCCCT GCGCACCCG CGGACGCTGG CCCTGGAGTG
901 CCCCTTCTGC CGCCGGGCCT GCGCGGGCTG CGACACCAGC GACTGCCTGC
951 CGGTGCTTCA CCTCTGGAG CTCCTGGGCT CGGCGCTGCG CCCAGCCCCC
1001 GCGCCCCCCC GCGCGGCCCG CCGCGCCGCC CCTGCGCCC CGGGCGCCCT
1051 CGCTGCCAT CACGCTTCG GAGGCTGGG GACCTGGTC AACCCACGG
1101 GGCTGGCGCT GTGCCCAAG ACCGGCGGG TCGTGGTGGT GCACGACGGC
1151 AGGAGGCGGG TCAAGATCTT TGA CTCCGGG GGAGGATGCG CCCATCAGTT
1201 TGGAGAGAAG GGGGAGGCTG CCCAGGACAT TAGGTACCCC CTGGACGTCG
1251 CCGTCACCAA GACTGCCAC GTGGTTGTCA CCGACGCCGG CGACCGCTCC
1301 ATCAAAGTGT TTGATTTCTT TGGCCAGATC AAGCTCGTCA TTGGAGACCA
1351 GTTTTCCTTA CCTTGGGCG TGGAGACCAC CCCTCAGAA TGGGTCTGTG
1401 TAACTGACGC CGAGGCAGGG TCGCTGCACC TGCTGGAAGT CGACTTTGCA
1451 GAAGGAGCCC TCCAGAGGAC TGAAGAGCTG CAAGGTCATC TGTGCAACCC
1501 GCGAGGGGTG GCGGTGTCCT GGCTCACTGG GGCCATTGCG GTCCTGGAGC
1551 ACCCTCCGGG GCTGGGGGCT GGGGCGGGCA GCACCGCGT GAAGGTGTTT
1601 AGCCCAACTA TGCAGCTGAT CGGCCAGGTG GATACCTTTG GGCTCAGCCT
1651 CTTTTTCCCC TCTAGAATAA CCGCTCCCG CGTGACCTTT GATCACCAGG
1701 GGAATGTGAT TGTTGCAGAT ACTTCTAGTC AGGCCGTCT ATGCTTGGGA
1751 CAGCCTGAGG AATTTCCAGT CCTGAAGCCC ATCATACCC ATGGTCTTTC
1801 CCATCCTGTG GCACTGACCT TCACCAAGGA GAATTCTCTT CTGTGCTGG
1851 ACAGTGACGC CCATTCCGTA AAAGTCTACA AGGCTGACTG GGGGTAA
```

SEQ ID NO: 3

11/15

Fig 7B

Met Gly Ala Glu Ala Ala Gly Ser Gly Arg Ala Leu Arg Glu Leu Val
1 5 10 15
Arg Glu Ala Glu Val Ser Leu Leu Glu Cys Lys Val Cys Phe Glu Arg
20 25 30
Phe Gly His Arg Gln Gln Arg Arg Pro Arg Asn Leu Pro Cys Gly His
35 40 45
Val Val Cys Leu Ala Cys Val Ala Ala Leu Ala His Pro Arg Thr Leu
50 55 60
Ala Leu Glu Cys Pro Phe Cys Arg Arg Ala Cys Arg Gly Cys Asp Thr
65 70 75 80
Ser Asp Cys Leu Pro Val Leu His Leu Leu Glu Leu Leu Gly Ser Ala
85 90 95
Leu Arg Pro Ala Pro Ala Ala Pro Arg Ala Ala Pro Arg Ala Ala Pro
100 105 110
Cys Ala Pro Gly Ala Leu Ala Cys His His Ala Phe Gly Gly Trp Gly
115 120 125
Thr Leu Val Asn Pro Thr Gly Leu Ala Leu Cys Pro Lys Thr Gly Arg
130 135 140
Val Val Val Val His Asp Gly Arg Arg Arg Val Lys Ile Phe Asp Ser
145 150 155 160
Gly Gly Gly Cys Ala His Gln Phe Gly Glu Lys Gly Glu Ala Ala Gln
165 170 175
Asp Ile Arg Tyr Pro Leu Asp Val Ala Val Thr Asn Asp Cys His Val
180 185 190
Val Val Thr Asp Ala Gly Asp Arg Ser Ile Lys Val Phe Asp Phe Phe
195 200 205
Gly Gln Ile Lys Leu Val Ile Gly Asp Gln Phe Ser Leu Pro Trp Gly
210 215 220

SEQ ID NO: 4

a

Towards malin's RING finger ← | → Towards malin's NHL domains

L R P A P A A P R A A P R A A P C A

Canis familiaris: CTGCGCCCTAGCCCCGGCCGCCCGCCCGCCCGCCCGCCCGCCCGTGC

D D T *

Mus musculus: CTCACGGGTCCCG-----GTCGCTCAGGCGCGCCCTTGCGG

Rattus norvegicus: CTCACGGGTCCCG-----GTCGCTCAGGCGCGCTCTGTGCG

Sus scrofa (Pig): CTTCGCGCGCGCC-----GGGCGCTCCCGCGCGCCCTCTCTTC

Homo Sapiens: CTTCGCGATGCCCG-----GCCGCCCATCGCGCGCCCTAGDGC

Pan troglodytes (Chimpanzee): CTTCGCGATGCCCG-----GCCGCCCATCGCGCGCCCTTAGDGC

b

W M C Non-deaminated DNA

W C C B C M C Deaminated DNA

c

Unaffected (n=2) Affected (n=3)

Felidae Canidae

d

Felidae Canidae

Canoidae Arctoidae

Species listed:

- Felis catus*
- Panthera leo* (Lion)
- Panthera tigris* (Tiger)
- Panthera pardus* (Leopard)
- Panthera uncia* (Snow Leopard)
- Acinonyx jubatus* (Cheetah)
- Lynx caescal* (Lynx)
- Canis familiaris*
- Canis lupus Dingo*
- Canis lupus* (Grey Wolf)
- Canis rufus* (Red Wolf)
- Canis latrans* (Coyote)
- Canis aureus* (Golden Jackal)
- Cuon alpinus* (Dhole)
- Dusicyon griseus* (Grey Fox)
- Urocyon littoralis* (Isl. Fox)
- Canepatus semistriatus* (Skunk)
- Ursus americanus* (Black Bear)
- Ursus maritimus* (Polar Bear)
- Ursus arctos* (Brown Bear)
- Ursus arctos horribilis* (Grizzly)
- Procyonide lotor* (Raccoon)
- Potos flavus* (Rinkajou)
- Bassaricyon beddardi* (Beddard)
- Nasua nasua* (Ringtailed Coati)
- Gulo gulo* (Weasel)
- Galictis vittata* (Grison)
- Mustela vison* (American Mink)
- Martes pennanti* (Fisher)
- Lutra canadensis* (Otter)
- L. maculicollis* (Spotted-neck Otter)
- Melogale moschata* (Chinese Ferret Badger)

Time scale: 60Ma, 50Ma, 10Ma

Fig 10

SEQ ID NOS: 6-52